Association between Lower Level Lead Concentrations and Hyperactivity in Children

by Oliver J. David*

Hyperactive children were compared with a nonhyperactive control group on two measures that reflect the presence of body lead and on a lead exposure questionnaire.

The overall hypothesis that was tested was that a relationship exists between hyperactivity in children and a concommitant condition of increased body lead stores. Operationally, the hypothesis was reduced to a comparison of the hyperactive group and control group on the following measures: (1) blood lead levels; (2) post-penicillamine urine lead levels; (3) scores on a lead exposure questionnaire. The designation hyperactive or nonhyperactive was arrived at by using three different measurements: a doctor's diagnosis; a teacher's rating scale; a parent questionnaire.

Hyperactive children had significantly higher values on all three measures than did the controls. More than half the hyperactive children had blood lead levels in the range considered to be raised but not toxic, and 60% of post-penicillamine urine levels were in the "toxic" range.

It is concluded that there is an association between hyperactivity and raised lead levels, that a large body-lead burden may exact consequencies that have hitherto been unrealized; that the definition of what is a toxic level for blood lead needs reevaluation and that physicians should look for raised lead levels in children with hyperactivity.

In the past two years, my colleagues and I have been concerned with the problem of low level lead toxicity and its possible association with hyperactive states in children. This problem divides naturally into two parts: first, to establish whether in fact, hyperactive children have higher levels of lead then their nonhyperactive brethren (*1*) and, second, if higher levels are found, to ascertain the nature of that association; that is, is an increased lead level a function of a child's being hyperactive or, is that higher lead level, in some way causally associated with the hyperactivity.

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We spent much of 1971–1972 evaluating the first of the two problems and it is this work, which will be reviewed in the present paper.

Hyperactivity is one of many terms used to describe a complex, multifacted syndrome. It is characterized by the fundamental behavioral manifestation of a high level of motor activity and is usually coupled with a short attention span, low frustration tolerance, and hyperexcitability (*2*).

It is convenient to divide children with hyperactivity into a school-age group and a preschool one. It is very rare to see a child with this problem before the age of three and it is most commonly seen in the school-age child (*3*). The presenting complaints of the preschool child are generally incessant activity leading to dangerous situations and inquisitiveness leading to accidental destruction (*3*). The school-age child is usually in constant difficulty at home because he is noisy, restless, and difficult to control. At school teachers are driven to distraction by his easy distractability, clowning and talking out of turn. He rarely finishes his work and as a result of all the above, is quite commonly and justifiably called a discipline problem (*3, 4*).

Studies done on hyperactive children have revealed that they have a variety of neurological and psychological abnormalities (*3, 5*). The neuropsychiatric characteristics cutting across this symptom complex can include abnormalities in perceptual-motor function, intelligence and achievement tests and tests of social maturity as well (*1*) as neurological "soft" signs and EEG abnormalities. It is important to note that none of these abnormalities need to be regarded as unequivocal evidence of major damage or abnormality of the CNS (*3*).

The question of causality regarding this syndrome is quite fluid. Retrospective studies commonly show that hyperactive children have in their background a much higher incidence of such events as: (a) abnormalities in the mother during the gestational period; (b) difficult delivery; (c) delayed resuscitation and/or other neonatal abnormalities, including low Agpar scores; (d) postnatal difficulties, such as head trauma, encephalitis, meningitis and other encephalopathies. In those children for whom no history of the above has occurred, the explanation for the disorder may be seen to be one or a combination of the following: an unrecognized or unrecorded cerebral insult, irregular maturation of the CNS, or a suspected but undefined maldevelopment of the brain (*6*).

Prevalence estimates of this and closely related disorders vary, some authorities going as high as 10–20% of our school population (*6*). If we hew closely to the prevalence of hyperactivity *per se*, approximately 5% of children in the U.S. alone may be suffering with this disorder.

At this point, I will review briefly a few of the specific suspicions mentioned in the literature prior to our work regarding associations between brain dysfunction and lower lead levels.

First, Stewart (*4*) has reported that he was "impressed with the frequency with which hyperactive children by history turn out to have had an incidence of accidental poisoning early in life, usually before the age of three." Stewart and others have explored and continue to explore the risk of occurrence, mortality, and morbidity of accidental poisoning in hyperactive children. It occurred to me that a second question can fairly be asked: namely, what is the risk of the occurrence of the hyperactive syndrome as a result of accidental poisoning—in this case lead poisoning.

Chisholm (*7*), in a review of chronic lead intoxication in children, asked the question: "What of a minor elevation of blood lead of long standing? Would it be involved in a cause-effect fashion with future neurologic dysfunction?" Hardy (*8*) presented the hypothesis that unimpressive blood lead levels and/or small amounts of lead, not now deemed clinically important, may interfere with enzyme systems if such poisoning occurs during the crucial developmental period of early childhood. When these children reach 6–7 years of age, Hardy predicts (*8*) many will appear in neurological clinics with various behavior disorders, although no reports of acute lead intoxication exist in their medical history. Byers (*9*) reviewed the development of his interest in childhood lead poisoning and stated that clinical observation made him believe that lead plays a deleterious role in the development of the CNS: ". . . I originally got interested in lead because of children who had had lead poisoning and had been sent home from the hospital cured, who then turned up in my neurological clinic because they were misbehaving in one way or another or not learning in school . . . none of these children had acute fulminating encephalitis. They all had evidence of lead-poisoning like stippled cells, some increase in spinal fluid total protein, gastro-intestinal symptoms and coproporphrin in the urine . . . when they reached six or seven, they showed evidence of neurologic injury" (*9*).

Miller and his associates (*10*), in a study on mentally retarded children showed that at blood lead levels from 20 to 40/μg/100 ml decreased δ-aminolevulinic acid dehydratase activity occurred. Their conclusion was that even "modest" levels of blood lead may be associated with biochemical abnormalities in children.

A review of the literature by Weiner (*11*) on the varying psychological sequela of lead ingestion in children concluded that while most studies reported some degree of mental impairment caused by lead poisoning, none of them showed definitely the existence or absence of a relationship between mental impairment and asymptomatic lead poisoning or lead poisoning less severe than that causing encephalitis. Despite the lack of definitive research "there is reason to believe that undiagnosed and therefore untreated lead poisoning, is a cause of concern."

In the light of these suspicions, therefore, our investigation was designed to ascertain whether hyperactive children have larger body lead stores than nonhyperactive control. The hypotheses tested were (1) hyperactive children will have significantly higher blood lead levels than nonhyperactive controls and (2) hyperactive children after challenge by a heavy metal chelating agent will have dramatically higher urine lead levels than controls subjected to the same challenge. To reach this last hypothesis we reasoned as follows. Lead ingestion, the primary mode of lead intake in children, usually occurs in the age group 1–5 years, but hyperactivity is most commonly diagnosed in somewhat older children, so blood lead levels in hyperactive children might not be high enough to reflect lead exposure happening several years earlier. To demonstrate this earlier exposure we decided to draw on bone stores of lead accumulated in the pica stage. We reasoned that a heavy metal chelating agent, such as penicillamine, would do this by competing with the body tissue ligands that bind lead. Penicillamine was chosen because of its comparatively low toxicity and because it could be administered orally. The technique used was a modification of that used by Ohlsson (*12*).

I should mention a rule-of-thumb equation regarding lead excretion time: that is, the time it takes a child to excrete lead is roughly twice the time of the ingestion period (*13*). For example, if a child of 1½ years begins to engage in lead pica and continues this activity until he is 4½, one should theoretically be able to find increased lead stores in him from age 1½ (when he started) until age 10½. Three years ingestion time $\times 2 = 6$ years plus 4½ (age when he stopped).

Methods

Hyperactivity Measures

Children were classed as hyperactive or nonhyperactive on the basis of a doctor's diagnosis, a teacher's rating scale (the Conner's scale (*14*), and a parent's rating scale (the Wherry-Weiss-Peters scale (*3*).

The doctor's diagnosis of hyperactivity was based on the presence of increased motor activity, poor impulse control, short attention span, hyperexcitability, and low frustration tolerance. The children in the nonhyperactive group had all been seen many times by many different physicians and at no time was a diagnosis of hyperactivity entertained. All the doctors' diagnoses were made without knowledge about lead levels.

The teacher's rating scale measures five behavioral factors, one of which is hyperactivity. Hyperactivity scores ranged from 1 ("not at all") to 4 ("very often"). Children were considered to be hyperactive if they achieved a mean score of 2.5 or more and nonhyperactive if their score was below 2.5. The parent's rating scale covers six major categories and asks the parent to score overactivity on a scale of 0 (none) to 4 (severe). Children were deemed hyperactive if their average score was 2.0 or more and nonhyperactive if their score was below 2.0.

If the three indices were not in accord, the two scores that did agree were used to designate the child hyperactive or nonhyperactive. If only two scores were available the teacher's score and then the doctor's diagnosis took precedence, in that order. If there was only one score then that one was used.

Exclusions

Children diagnosed as psychotic or who had evidence of significant neurological disease were excluded.

Children with hyperactivity and an event in their background thought to be a cause of this condition were considered separately from those with no such history. These events were broken into "possible" causes and "highly probable" causes, and these groups were analyzed separately. Of the 191 children examined, after the above exclusion processes the following groups emerged (Table 1): (1) a hyperactive group without psychosis or neurological disease and *with no evidence of an event known to be* associated with the development of hyperactivity ("pure" hyperactive), (2) a hyperactive group without psychosis or severe neurological disease but where a "highly probable" cause for hyperactivity existed (e.g., a child weighing 1600 g at birth with an ABO incompatibility occasioning a total exchange transfusion); (3) a group similar to group 2 but differing in that the event thought responsible for hyperactivity was considered not "highly probable" but "possible" (e.g., a child whose mother had been anemic during pregnancy); (4) a group of children with a history of lead poisoning. All children in this group had been treated at least 5 years previously (with one exception). Five of the eight children in this group were just hyperactive, three had neurological conditions of mild-to-moderate diffuse brain damage, one with mental retardation. In addition, there was a nonhyperactive control group judged on the same criteria as for the hyperactive group.

General Characteristics of the Population

All the children were seen as outpatients in one of three clinics in the Kings Country Hospital-Downstate Medical Center complex, which serves Brooklyn, N.Y. These three clinics were a pediatric neurology unit, a general pediatric clinic, and a research psychopharmacology unit. This complex sees about 145,000 children as outpatients in a year. The breakdown of this population is as follows (*15*): 61% male, 39% female; 62% black, 38% white (a large proportion of the white population is Puerto Rican); 73% U.S. born, 12% Puerto Rican, 15% other or unknown. Data on status are not available, but of the 98% of the population living in Brooklyn, 53% reside in East New York and Bedford-Stuyvesant (areas among the most impoverished in the city), 11% live in generally middle-class areas, and most of the rest come from impoverished areas similar to Bedford-Stuyvesant and East New York.

The children we examined were typical of this population, except that our hyperactive population was even more predominantly

Table 1. Details of groups studied.

Group	No.	Age, yr			M/F	Mean hyperactivity score	
		Mean	S.D.	Range		Teacher	Parent
"Pure" hyperactive	54	7.8	2.04	3½–11	43/12	3.2	3.2
Highly probable cause for hyperactivity	9	7.3	2.25	4–10	8/1	2.8	2.7
Possible cause for hyperactivity	11	7.7	1.28	6–10	9/2	3.1	2.1
History of lead poisoning	8	7.3	1.73	3½–9	8/0	3.5	3.4
Controls	37	7.6	2.14	3½–12	27/10	1.6	0.8

male than the general clinic population, so we chose more male controls than a simple random selection would have provided. The two clinics from which most of the hyperactive subjects came contained a very small number (4–5%) who came from areas outside Brooklyn to get the benefit of a university-based clinic. Thus, this very slight difference in socioeconomic basis would be in the direction of a slightly higher socioeconomic level in the hyperactive population.

Laboratory Data

Blood Lead Levels

Two 5-ml specimens of blood were obtained from each child, and a separate blood determination was done on each specimen. Blood lead levels were measured by the atomic absorption spectrophotometry method of Hessel (*16*). The standard deviations for this analysis are ± 3.97 μg/100 ml at a 30 μg/100 ml concentration and ± 5.68 μg/100 ml at a 60 μg/100 ml concentration. The laboratory mean for 60 specimens containing 30 μg was 30.69 μg/100 ml, and the mean on unknowns containing 60 μg/100 ml was 60.85.

Urine Lead Levels

The parents of almost all children (children with a history of penicillin allergy were excluded) were asked to give their child 250 mg penicillamine just before bedtime, collect the first urine voided in the morning, and to bring that specimen to the hospital on the same day. Informed parental consent was obtained in every case by using a form that was signed by a parent. The consent form stated what we were doing and the dangers involved. The method used for the urine analysis was that used routinely by the Lead Poison Division of the Bureau of Laboratories in New York City. The Bureau does not have figures on the errors of measurement for urine lead determinations done in their laboratory.

Results

The data were analyzed on comparing the normal control group with each of four groups: (1) the hyperactive group in whom no psychosis or major neurologic disease existed and in whom no known history of an etiologic event thought to be associated with hyperactivity was present, (2) the group with a "highly probable" cause for hyperactivity, (3) the group with a "possible" cause for hyperactivity, (4) the group in whom the "highly probable" cause for hyperactivity was a documented history of overt lead poisoning.

For each experimental group the blood lead levels, and urine lead levels were compared to those of the control groups (Table 2). The "pure" hyperactives are significantly different from the control group on these (*2*) measures.

Table 2. Blood lead and post-penicillamine urine lead levels in four groups of hyperactive children compared with nonhyperactive controls.

	Blood lead			Post-penicallimine urine lead		
Group	No. tested	Mean S.D., μg/100 ml	P [a]	No. tested	Mean S.D., μg/l	P [a]
"Pure" hyperactive	54	26.23±8.41	<0.01	50	146±144	<0.025
History of lead poisoning	8	41.06±12.18	<0.001	4	325±167	<0.001
Highly probable cause of hyperactivity	9	22.89±6.60	N.S.	5	46±32	N.S.
Possible cause for hyperactivity	8	29.94±7.35	<0.01	9	189±155	<0.01
Controls	37	22.16±9.59	—	24	77±92	—

[a] Students t test (one tail).

The mean blood lead level in this hyperactive group was 26.23 μg/100 ml, and that of the control group was 22.16 μg/100 ml (P) <0.01). The mean values for the post-penicillamine urine lead level are 77 μg/l. in the control group and 146 μg/l. in the hyperactive group ($0.25 < P < 0.01$).

The results indicate that the "pure" hyperactive subjects had higher blood lead levels, and urine lead levels than the control subjects.

The group of experimental subjects with a "possible" cause for their hyperactivity showed a similar pattern of significantly elevated blood and urine lead levels (Table 2) (both P values <0.01). The hyperactive subjects had a mean blood lead level of 29.94 μg/100 ml (controls 22.16 μg/100 ml); mean urine lead levels of 189 μg/l. (control 77 μg/1.).

In contrast to these two groups were the results for the hyperactive subjects with a highly probable cause of their hyperactivity (Table 2). On these two measure they showed no significant difference from the controls. The mean blood and urine lead levels were 22.89 μg/100 ml and 46 μg/l., respectively. The comparable scores for the controls were 22.16 μg/100 ml and 77 μg/l. This rather clearly indicates that lead level is not ubiquitously related to hyperactivity.

Finally, the group with a history of lead poisoning was compared to the normal control group (Table 2). The means for this group were 41.06 μg/100 ml mean blood lead level, and 325 μg/l. mean urine lead level. The difference between the means of this group and that of the control group easily reached the 0.001 level of significance on both measures.

The range and frequency distribution of these findings were also analyzed in the light of what are now considered to be normal, marginal, and toxic levels. Frequency analyses of these measures for each group of hyperactive subjects are presented in Table 3. For the blood and urine measures, χ^2 analyses were performed comparing the pure hyperactive group and the control group in terms of the proportion of subjects having normal or elevated values. (A normal blood lead value is here defined at 24.5 μg/100 ml or less; a normal urine lead level was defined as 80 μg/l. or less.)

An examination of Table 3 shows that for the normal control subjects 75% had "normal" blood lead levels and 27% were in the elevated range. In the pure hyperactive group, 52% showed elevated blood lead values and 48% were within normal range. A chi-square analysis with one degree of freedom indicates that the probability of this frequency happening by chance is $0.02 > P > 0.01$. Post-penicillamine urine lead scores for these two groups show that 62% of hyperactive children had elevated levels while only 21% of the controls had elevated levels. Of the normal subjects 79% had urine levels within normal limits, while this was true for only 38% of the "pure" hyperactive subjects. A chi-square analysis indicates that the probability of this occurring by chance is $P > 0.001$.

The frequency analysis of blood lead levels and urine lead levels for the "possible cause" group was as follows: 62.5% had elevated blood lead scores and 78% had elevated urine lead scores (Table 3).

The last group compared to the normal controls is the hyperactive group whose ("highly probable" reason for hyperactivity is a documented past history of overt lead poisoning. The frequency of elevated blood and urine scores in this group is 100%.

Discussion

Lin-Fu (*17*) has commented on some of the erroneous concepts regarding "normal" blood lead levels. One of the points she makes is that most papers equate the lowest blood lead level diagnostic of clinically manifest lead poisoning with the upper limits of normal. A level not associated with overt clinical evidence of toxicity surely does not have to be normal. "Symptoms from low level lead intake may for example be overlooked because no one knows what to look for. Thus, children are considered asymptomatic because classic symptoms and signs of lead poisoning are absent." She

Table 3. Frequency of raised blood lead and post-penicillamine urine lead levels.

Group	No. of children with blood lead levels in various ranges						No. of children with urine in various ranges			
	5–14.5 μg/100 ml	15–24.5 μg/100 ml	25–34.5 μg/100 ml	35–44.5 μg/100 ml	45–54.5 μg/100 ml	55–64.5 μg/100 ml	0–80 μg/l.	81–160 μg/l.	161–240 μg/l.	>241 μg/l.
Pure hyperactive	4 (7%)	22 (41%)	19 (35%)	7 (13%)	2 (4%)	0	19 (38%)	19 (38%)	4 (8%)	8 (16%)
History of lead poisoning	0	0	3	3	0	2	0	0	1	3
Highly probable cause for hyperactivity	0	5	3	1	0	0	4	1	0	0
Possible cause for hyperactivity	0	3	3	1	1	0	2	4	1	2
Controls	4 (11%)	23 (62%)	6 (16%)	4 (11%)	0	0	19 (82%)	3 (13%)	1	1

goes on to cite various studies that define varying blood lead levels from 80 $\mu g/100$ ml to 20 $\mu g/100$ ml as upper limits of normal. It is, however, fair to say that over the years the "mainstream" concept of what the upper limit of normal is has been dropping. At present most authorities agree that a blood lead value below 24.5 $\mu g/100$ ml is normal and a value above 55 $\mu g/100$ ml is abnormal (although not necessarily requiring treatment). Our findings suggest that the arguments for considering any lead elevation above 24.5 $\mu g/100$ ml as dangerous should receive serious attention.

A massive single dose of lead can result in death or severe brain damage, and in many cases a large dose of lead ingested over a period of time can also lead to very severe brain damage. It seems reasonable to infer, therefore, that raised levels of lead (not necessarily in the toxic range) present over a long period could be responsible for the minimal brain damage that may be present in the hyperactive syndrome.

Our finding of raised post-pencillamine lead levels in urine in combination with the high blood lead values indicate that many hyperactive children have had increased body lead stores for a long time. It is conceivable that one consequence of this constant minimal poisonous assault is hyperactivity. If we hold lead exposure responsible for some cases of hyperactivity (an assumption only), we might predict the following: (1) there would be little difference in lead values between the normal control group and the "highly probable cause" group (i.e., the group with a likely cause for hyperactivity other than lead); (2) the "pure" hyperactive group and the "possible" group would both show raised lead levels. (The "possible" group differs from the "highly probable" group in the crucial distinction of a convincing other cause for hyperactivity being absent.) These predictions are supported by the results.

All eight hyperactive children who also had a history of lead poisoning had elevated blood and urine lead levels at the time of the study. All but one had been treated with chelating agents at least 5 years previously. This finding indicates that the treatment of these lead-poisoned children may not have been extensive enough and/or that follow-up procedures had been unsuccessful. It may also mean that hyperactivity heretofore thought to be a relatively common consequence of lead poisoning is not necessarily a consequence at all, but a condition that is dependent on continuing elevations (nonlethal) of body lead.

Might the lead levels recorded be a consequence of the child's hyperactivity rather than a hyperactivity cause? This interpretation is not supported by the finding that the "highly probable cause" hyperactive group do not show increased blood or urine lead levels. There are, however, too few children in that group to arrive at a definite conclusion.

Hyperactivity is a symptomatic state, not a disease. Being able to segregate a group of such children in whom the etiology is known (e.g., due to lead) would be extremely helpful and might be useful in further research of the hyperactive child syndrome. Despite the lack of proof of a causal relation between the hyperactivity and lead, blood lead levels and post-penicillamine urine lead levels should be routine investigations in cases of hyperactivity.

Before ending this discussion, a word must be said concerning the social and environmental implications of this work. It will be remembered that estimates concerning the prevalence of hyperactivity range from 5% of our child population on up. If we estimate the child population to be roughly 20–25% of the total, we find that 5% of this is approximately 2,000,000 people. It is conceivable that via the findings contained herein, the possibility of a direct amelioration of that condition is possible in fully, 1,000,000 children. What this might mean in terms of immediate treatment and the avoidance of complicating social and personal sequelae and in public health terms is staggering.

REFERENCES

1. David, O. J., Clark, J., and Voeller, K. Lead and hyperactivity. Lancet (2): 900 (October 28, 1972).
2. Millichap, J. G. Hyperactive behavior, learning disabilities, and minimal brain damage. Proc. Inst. Med. Chicago, Chicago Pediatr. Soc. 27 (10): 277.
3. Wherry, J. S. Developmental hyperactivity. Pediatr. Clinics North Amer. 15: 581 (1968).
4. Stewart, M. A. Hyperactive children. Sci. American 222 (4): 94 (1970).
5. Laufer, M. W., Denhoff, E., and Solomon, G. Hyperkinetic impulse disorder in children's behavior problems. Psychosomatic Med. 19: 38 (1957).
6. Paine, R. S. Syndromes of "minimal cerebral damage," Pediatr. Clinics North Amer. 15: 779 (1968).
7. Chisholm J. J. Jr. Chronic lead intoxication in children. Devel. Med. Child Neurol. 7: 529 (1965).
8. Hardy, H. L. What is the status of knowledge of the toxic effect of lead on identifiable groups in the population (Editorial). Clin. Pharmacol. Therapy 7: 713 (1966).
9. Byers R. R. Round table discussion of presentation by E. L. Belknap. Clinical control of health in the storage battery industry. In: Proceedings of the Lead Hygiene Conference, Chicago, 1958. Lead Industries Association, Chicago Ill. 1958, p. 73.
10. Millar, J. A., Battistine, V., Cumming, R. L. C., Cornwell, F., and Goldberg, A. Lead and δ-aminolaevulinic acid dehydratase levels in mentally retarded children and in lead-poisoned suckling rats. Lancet (2): 695 (1970).
11. Wiener, G. Varying psychological sequaelae of lead ingestion in children—a review of the literature. Public Health Reports 85: 19 (1970).
12. Ohlsson, W. T. Occup. Health Rev. 15: 14 (1963).
13. Chisolm, J. J., and Kaplin, E. Lead poisoning in childhood—comprehensive management and prevention. J. Pediatr. 73: 942 (1968).
14. Conners, C. K. A teacher rating scale for use in drug studies with children. Amer. J. Psychiat. 126: 884 (1969).
15. New York City, Department of Hospitals. Population served by Kings County Hospital. Hospital Statistic Service, Note, 1970.
16. Hessel, D. W. A simple and rapid determination of lead in blood. Atomic Absorption Newsletter 3: 55 (1968).
17. Lin-Fu, J. S. N. Engl. J. Med. 236: 702 (1972).